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By Zachary Ziliak

The National Institute of Health announced Aug. 4 that it would not authorize generic competition for Abbott Laboratories' AIDS drug Norvir, also known as ritonavir. Essential Inventions, a not-for-profit consumer advocacy group, had petitioned the NIH to grant such authorization after Abbott increased the price of a daily dose of Norvir from $1.71 to $8.57.

Essential Inventions based its request on the Bayh-Dole Act of 1981, which clarifies control rights over inventions resulting from public-private partnerships.[1] Under Bayh-Dole, firms receiving federal research funding retain title over resulting inventions.[2] However, the funding agency may "march in" and force the patent-holder to issue licenses to other companies to ensure the practical application of the invention and its availability to the public on reasonable terms.[3]

Between 1988 and 1993, Abbott received almost $3.5 million from the NIH to assist with its research into protease inhibitors to fight HIV, the virus that causes AIDS. Protease is an enzyme that HIV needs in order to infect new cells; protease inhibitors block the protease enzyme. Abbott's research led to the development of ritonavir. The FDA approved ritonavir for widespread treatment of HIV in 1996, and Abbott now markets ritonavir under the brand name Norvir. "The whole relationship and how it led to the discovery can be viewed as a Bayh-Dole success story," said Abbott spokeswoman Jennifer Smoter.

Abbott originally marketed ritonavir as a stand-alone HIV drug with dosages of up to 1200 mg per day. However, later studies revealed that ritonavir impeded the metabolism of various other protease inhibitors, thereby extending their half-lives in the body. As a result, HIV patients now commonly rely on drug "cocktails" consisting of 50 mg to 200 mg of ritonavir and a larger dose of another, less noxious protease inhibitor. The ritonavir "booster" improves the effectiveness of the primary protease inhibitor.

With daily ritonavir dosage thus falling from 1200 mg to roughly 100 mg, Abbott responded in December 2003 by quintupling the price of Norvir. Essential Inventions, together with members of Congress, including Rep. Sherrod Brown (D-Ohio), asked the NIH to exercise its Bayh-Dole "march-in" rights, arguing that at its new price point, Norvir was no longer available to the public on reasonable terms.

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After taking statements from advocates on both sides, the NIH ruled that Abbott had indeed "met the standard of achieving practical application of the applicable patents." More generally, the NIH stated that Bayh-Dole should not be used to monitor pricing. Such concerns would more properly be addressed to the Federal Trade Commission. Robert Weissman, general counsel for Essential Inventions, announced that the organization would appeal the decision.

In its request to the NIH, Essential Inventions contended that the Norvir price increase would directly affect consumers. Robert Huff of Gay Men's Health Crisis, a not-for-profit group aimed at reducing the spread of HIV, called the Norvir price increase "an egregious example of changing the price on something and making it unaffordable to a lot of people."

Abbott responded that both before and after the price increase, Norvir's daily cost was the lowest of any protease inhibitor on the market. Still, some questioned Abbott's comparison, noting that Norvir was more expensive than other protease inhibitors if taken at its stand-alone dose. On June 10, 2004, the FDA's Division of Drug Marketing, Advertising and Communication called Abbott's argument "mis-

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leading" for that reason.

Abbott further asserted that no patients would actually pay more for Norvir than before December 2003. Abbott froze the price of Norvir for government AIDS programs and committed to giving Norvir free to all patients not covered by insurance or a government program.

Smoter reported a fast start to Abbott's Patient Assistance Program. "We've been able to process hundreds of applications this year already," she said.

GMHC's Huff acknowledged that the Norvir Patient Assistance Program reduced the harm to patients. "We're still looking for individual patients who have been directly denied, and we haven't found them, so it seems to be working," he said. Huff, however, remained concerned about the delay in processing applications for the Patient Assistance Program. "For AIDS, you can't go two weeks without your drugs," he said.

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Essential Inventions also argued that Norvir's price increase could harm patients indirectly by reducing the incentive for companies to research drugs that must be used in combination with ritonavir. As Huff explained, the price hike "really sent a chill through some drug development programs from other companies. There's no point developing a drug that depends on Norvir."

To mitigate such effects, Abbott froze the price of Norvir for companies researching protease inhibitors for use with ritonavir. However, the freeze expires when the new protease inhibitors gain FDA approval. Thus, research costs would not be affected, but the market price of the cocktail would still rise. "Adding Norvir to what they want to charge will make this just astronomical," said Huff.

Finally, Essential Inventions questioned Abbott's pricing of Kaletra, an all-in-one protease inhibitor cocktail. Like other cocktails, Kaletra consists of a primary protease inhibitors, lopinavir, together with a smaller dose of ritonavir as a booster. However, as lopinavir and ritonavir are very similar chemically, Abbott claims that their interplay exceeds that of other cocktails.

Abbott decided to leave the price of Kaletra unchanged while increasing the price of Norvir. Essential Inventions called Abbott's decision anti-competitive. It argued that patients who preferred a different primary protease inhibitor would now have to pay more for their ritonavir booster, while those using lopinavir would incur no price increase. By bundling lopinavir with ritonavir, Abbott was attempting to leverage its ritonavir monopoly into control over the primary protease inhibitor market, Essential Inventions said.

Abbott rejected Essential Inventions' link between Kaletra and Norvir. "We didn't change the price of Kaletra, because the use of that drug has not changed," explained Smoter. Moreover, the hypothesized shift to Kaletra has not materialized, with Kaletra's market share remaining unchanged over the past three quarters.

Such observations struck a chord with some groups that had earlier questioned Kaletra's price. Despite a letter from Senators Charles Schumer (D-N.Y.), John McCain (R-Ariz.), and Ernest Hollings (D-S.C.) requesting an antitrust investigation, the FTC decided not to study the Norvir-Kaletra pricing issue, Abbott reported recently.

Others, however, continue to raise questions. The attorneys general of New York and Illinois both declared their intention to investigate the matter.

Essential Inventions' Weissman cautioned that since switching protease inhibitors can shorten the time they remain effective, patients generally stick with one as long as it works. Weissman thus predicted a gradual increase in Kaletra's market share as patients come off their old drugs and have to pick a new one. "It might not happen immediately, as there are serious consequences to bouncing around among treatments," he said. "As people do switch because they burn through the regimen and become infected, the pricing decision is certainly going to have an impact."

GMHC's Huff likewise predicts that "we haven't seen all the impact of this yet."

The Norvir controversy exemplifies a long-standing policy debate surrounding Bayh-Dole. Producers of generic drugs lobby for more zealous

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marching in by the government. If federal agencies never act, they argue, recipients of federal research grants will be free to impose monopoly prices on consumers. Pharmaceutical researchers counter that federal funds represent a tiny percentage of the cost required to bring a drug to market. In the case of Norvir, for instance, the NIH contributed $3.5 million to Norvir's development compared to more than $300 million from Abbott. Research firms argue that if one percent of federal funding suffices to undermine a company's patent protection, firms will stop applying for federal grants.

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Because one of the primary goals of the Bayh-Dole Act is "to encourage maximum participation ... in federally supported research and development efforts,"[4] the NIH has preferred to err on the side of caution. To date, neither the NIH nor any other federal agency has ever curtailed a research firm's patent protection by marching in. "You don't want to kill the golden goose," said Joseph Allen, president of the National Technology Transfer Center.

Much of the debate leading up to the NIH's decision concerned Bayh-Dole's use as a tool to police pricing. In an article not specifically addressing Norvir, Professors Peter Arno and Michael Davis pointed to several extracts from the Congressional debates over Bayh-Dole that appeared to target price regulation.[5] In their words, "Congress's concern with march-in rights focused exclusively on maintaining competitive conditions, controlling profits, and doing so through price control."[6]

However, former Sen. Birch Bayh (D-Ind.), one of the original sponsors of the law, told the NIH that the law was aimed at ensuring companies would develop inventions, not at allowing the government to set prices. GMHC's Huff acknowledged that march-in advocates could not hang their hats on explicit statutory language. A provision for price controls "was not written into the final form, because it probably wouldn't have passed," said Huff.

Absent explicit pricing language in the law, Essential Inventions and its supporters urged the NIH to interpret the "reasonable terms" test to include price. Weissman maintained that any other interpretation would undermine the goals of Bayh-Dole. "It's hard to imagine what reasonable terms means if it doesn't include price," Weissman said. Huff added, "If you think about what potential barriers are to access, price definitely can be included as a barrier. I think they could have stretched it."

Pharmaceutical companies feared such price controls, especially absent clear legislative backing. Only a very small portion of the drugs that companies research receive FDA approval, they argued, and revenues from those few success stories must fund research in many more compounds. "We have to make sure we realize the value of the drugs we have on the market today, so that we can develop future generations of medicines," said Abbott's Smoter.

The Bayh-Dole Act grants patent-holders the right to appeal decisions to the U.S. Court of Federal Claims.[7] While the act provides for no appeal of rejection of march-in petitions beyond the funding agency, Essential Inventions and Rep. Brown have asked the Dept. of Health and Human Services to review the NIH's decision.

"It is difficult to conceive of more unreasonable terms than a 400 percent price increase jerry-rigged to stifle competition and imposed only on one set of consumers-American consumers," Brown wrote.

1. 35 U.S.C. §§ 200-212 (2004).
2. § 202(a).
3. §§ 201(f), 203(1)(a).
4. 35 U.S.C. § 200.
5. Peter S. Arno & Michael H. Davis, *Why Don't We Enforce Existing Drug Price Controls?*, 75 Tul. L. Rev. 631, 662-66 (2001).
6. *Id.* at 659.
7. 35 U.S.C. § 203(2).